

X-linked mental retardation and severe short stature with a novel mutation of the *KDM5C* gene

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Abstract. Many monogenetic disorders of short stature have autosomal recessive/dominant form of inheritance. However, X-linked short stature has not been well recognized. Herein, we report a case of a boy from a family with familial severe short stature and mental retardation, who displayed an X-linked recessive trait. The boy at the age of 4 yr and 6 mo presented with remarkable growth failure (height: 76.5 cm [−6.3 SD]) and mental retardation (IQ: 30) and cerebellar volume loss and without an external anomaly or microcephaly to our hospital. A careful interview to determine the family history suggested a genetic background of familial mental retardation and short stature. His mother had mild intellectual disability with normal stature and his maternal uncle had severe mental retardation with remarkably short stature. Whole-exome sequencing identified a pathogenic variant in the *KDM5C* gene, NM_004187: exon 23: c.3874_3875del: (p.Ala1292Glnfs*7). He presented with a novel frameshift mutation. His mother was a heterozygous carrier of the variant. This case suggests that a disorder associated with the *KDM5C* gene should be considered when patients present with remarkably short stature and X-linked mental retardation.

Key words: *KDM5C* gene, X-linked mental retardation, short stature, cerebellar hypoplasia

Introduction

Short stature is defined as height below the 3rd percentile for the chronological age or −2 SD of the corresponding mean height for a given age, sex, and population. The pathogenesis is heterogeneous, including environmental exposure to infection, drugs, chemical compounds, or genetic factors involving largely unknown genetic variants (1). A recent genetic study identified several genes associated with monogenic disorders of short stature, including genes contributing to the proliferation of growth plate chondrocytes, such as *SHOX*, *NPR2*, *NPPC*, *FGFR3*, and *ACAN*, and genes associated with GH/IGF-1 secretion and intracellular signaling, such as *GHI*, *GHR*, *GHSR*, *IGFALS*, and *STAT5B* (2). Many of the monogenic disorders of short stature are inherited as autosomal recessive or dominant traits. A defect in the *SHOX* gene, located on Xp22.33, has an autosomal dominant mode of inheritance because it is located within the pseudoautosomal region in the X chromosome (3). However, X-linked idiopathic short stature has not been well recognized.

Mental retardation (MR) is a relatively common

neurological disorder with an estimated prevalence of 2–3% in developed countries. Its causes are heterogeneous and include environmental exposure with a background of genetic predisposition. In the general population, it is more common in males than in females, indicating the presence of many causal genes on the X chromosome. A recent study revealed that up to 100 different genes might be involved in X-linked MR (XLMR) (4, 5). Genetic defects of the *KDM5C* gene are a relatively common cause of XLMR and are associated with growth failure of variable severity (6).

Herein, we report a case of a boy with a novel pathogenic variation in the *KDM5C* gene; he hailed from a family with familial severe short stature and MR, which proved to be a X-linked recessive trait.

Case Report

A Japanese boy was born by vaginal delivery at 38 wk of gestation. His birth weight was 3,365 g (79.8th percentile), birth height was 48.0 cm (34.7th percentile), and head circumference was 34.5 cm. He presented with a borderline level of mental development and achieved

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the milestones of holding his head-up at 3 mo and sitting up by self at 8 mo. However, he showed remarkable growth failure (height -4.0 SD) at 18 mo of age. His development scores were not evaluated at this time. He did not have a peculiar face and showed no external anomalies. He had not attended regular checkups at our hospital for two years. At 4 yr and 6 mo of age, the boy presented to a local health care center and was then admitted to our hospital to investigate the cause of his growth failure and MR (**Fig. 1**). His height was 76.5 cm (-6.3 SD), and his head circumference 47.5 cm (-1.9 SD). He did not speak any words. Physical examination demonstrated marked spasticity in the lower extremities and increased patellar tendon reflex. He was able to walk alone without disequilibrium. His development scores evaluated based on the Enjoji Scale of Infant Analytical Development were as follows: movement developmental quotient (DQ), 27; sociality DQ, 38; and language DQ, 24. A careful interview of the parents was conducted to investigate the patient's family history, and it suggested a genetic background of familial MR and short stature; his mother appeared almost normal in stature with only mild intellectual disability (roughly at the level of a 15-yr-old girl, according to the physician's impression). His maternal uncle had severe MR (he did not speak words spontaneously) with remarkably short stature (< 150 cm). The boy's brother and sister showed normal physical growth and mental development (**Fig. 2**).

The biochemical parameters were all within the normal range, including the serum or plasma levels of lactic acid, pyruvic acid, very long chain fatty acids, amino acids, and hormones including IGF-1, TSH, FT4, LH, FSH, and testosterone. Analysis of urinary

mucopolysaccharides and organic acid did not reveal abnormal metabolites. Brain magnetic resonance imaging demonstrated cerebellar volume loss (**Fig. 3**). Chromosomal analysis showed a normal karyotype of 46, XY. We performed whole-exome sequencing (WES). DNA was obtained from the peripheral blood samples of the patient, his mother, sister, and brother. No sample could be obtained from his father because his parents were divorced and had been out of social contact for some time. WES was performed using a SureSelectXT Human All Exon V6 (Agilent Technologies, Santa Clara, CA, USA) on a HiSeq 2500 platform (Illumina, San Diego, CA, USA). We narrowed down the variants with an allele frequency of $< 0.1\%$ based on variant data obtained from the 1000 Genomes (<https://www.internationalgenome.org/>), HGVD (<http://www.hgvd.genome.med.kyoto-u.ac.jp/>), and 3.5 KJPN (<https://jmorp.megabank.tohoku.ac.jp/>) databases and an in-house database. Dominant and recessive modes of inheritance were both assumed for the analysis among the proband, his mother, and a healthy sibling. The Online Mendelian Inheritance in Man (<http://www.omim.org>) and PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) databases were used to identify any known disease associations. As a result, a pathogenic variant in the *KDM5C* gene, NM_004187: exon 23: c.3874_3875del (p.Ala1292Glnfs*7) was proposed as the disease causing mutation in association with the patient's phenotypes of short stature and MR (**Fig. 1**). His mother was a heterozygous carrier of the variant; his sister did not have the variant. It was predicted that the maternal uncle would have the same variant; however, a genetic analysis was not performed.

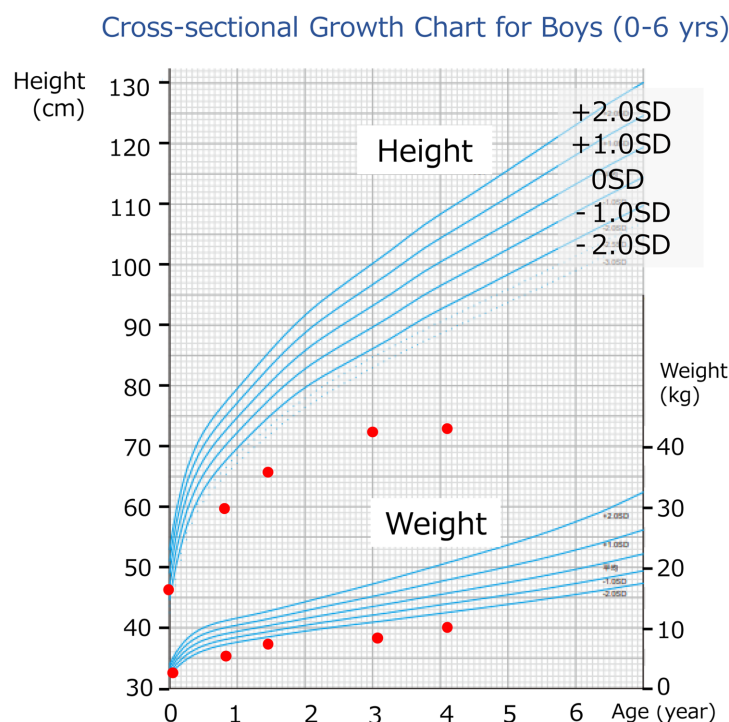


Fig. 1. Growth chart of the patient

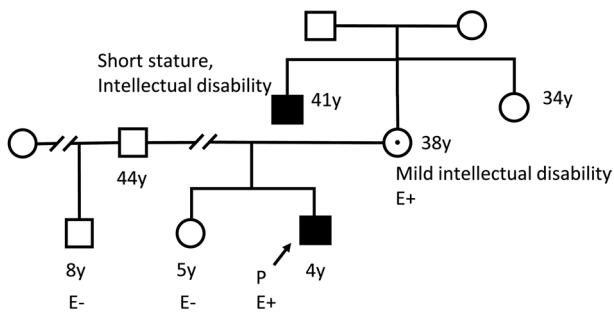


Fig. 2. The pedigree of the family. The patient and his maternal uncle presented with remarkably short stature and intellectual disability. The mother had mild intellectual disability. E+: Affected individual with positive evaluation. E-: Individual with negative evaluation. P: Proband

This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the institution (approval number: P-15-08). Written informed consent was obtained from the patient's family prior to the collection of blood samples from the patient and his family members.

Discussion

We report the case of a boy with severe short stature and XLMR due to a mutation in the *KDM5C* gene, which is located in a non-pseudoautosomal region (7). The *KDM5C* protein functions as a histone-3-lysine-4 (H3K4) demethylase and is involved in the demethylation of H3K4me3 and H3K4me2. The gene is related to epigenetic regulation and chromatin remodeling (8, 9). A previous report demonstrated that clinical evaluation did not reveal any consistent phenotype, with the exception of a mild-to-severe MR (100%) (10). Most affected individuals had short stature (55%) and hyperreflexia (78%); a minority had seizures (33%) and aggressive behavior (44%) (11). Mutations in the *KDM5C* gene were also associated with microcephaly, and a missense mutation was reported in a patient with autism spectrum disorder (12). Female carriers did not have any features; however, some family members of female carriers showed a mild phenotype. A weak phenotype-genotype correlation has been reported (11). Missense mutations in the JmjC domain cause a partial loss of the H3K4 histone demethylase activity of *KDM5C* and affected individuals have moderate intellectual impairment, short stature, and microcephaly. However,

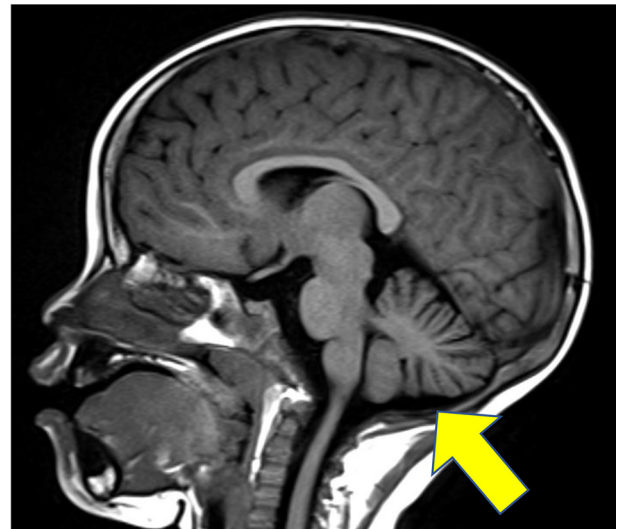


Fig. 3. T1-weighted brain MRI recorded at 4 yr of age. Arrow indicates cerebellar volume loss.

those with mutations in and around the C5HC2 domain tend to have severe intellectual impairment. A nonfunctional frameshift mutation causes severe intellectual impairment and epilepsy with mild dysmorphic features. In addition, phenotypic variations in carriers of X-linked disorders have been attributed to a pattern of skewed X-chromosome inactivation; hence, females with mutations in the *KDM5C* gene can have variable manifestations. Clinical features of patients with *KDM5C* mutations have been described in previous papers or their supplementary data (5, 6, 10–15), and *KDM5C* mutations with MR has been reported in several Japanese families (5, 15). The present case with a novel frameshift mutation presented with severe short stature and MR with cerebellar volume loss and without any external anomaly or microcephaly. Further studies including more cases will be necessary to establish the genotype-phenotype correlation in Japanese patients with pathogenic variants of the *KDM5C* gene.

Conclusion

Genetic disorders associated with the *KDM5C* gene should be considered in patients presenting with remarkably short stature and XLMR.

Conflicts of interest: The authors declare no conflicts of interest in association with the present study.

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